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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,936	08/16/1999	HERMANN OPPERMAN	STK-077	4340

21323 7590 06/16/2003
TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT PAPER NUMBER

1647

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/374,936	Applicant(s) OPPERMANN ET AL.	
	Examiner Jegatheesan Seharaseyon	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/19/02 & 3/19/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5 and 6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-3,5 and 6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This Office Action is in response to Applicant's remarks and amendment filed on 3/19/03. The Office will withdraw the restriction/species requirement of 11/19/02 (Paper No: 21) and reinstate the restriction requirement of 12/14/00 (Paper No: 8) as indicated by the Office Action of 3/11/02 (Paper No: 16). The prosecution on the merits of claims 1-3, 5 and 6 continues to the extent that they read upon the elected invention.
2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, withdrawn

3. Rejection of claims 1, 2, 5 and 6 as indefinite under 35 USC § 112 2nd paragraph is withdrawn in view of Applicant's arguments and amendments filed on 8/29/02.

Claim Rejections - 35 USC § 103, maintained

4. Rejection of claims 1-3, 5 and 6 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Keck et al. (a12) in view of Griffith (v120, Luyten (n12), Qian (u12), Daopin et al. (w12). Applicant's arguments filed on 8/29/02 have been considered but are not persuasive. Applicants argue that the references either alone or in combination do not render the claims obvious over Keck in view of Griffith, Luyten, Qian or Daopin. This not found to be persuasive for reasons of record in Paper No: 12 and paper No: 16. In addition, applicant argues that the examiner's rejection amounts to no more than an "obvious to try" standard. The applicant further argues that at the time of filing this application, it would not have been obvious to the skilled worker to swap the sub domains of a TGF- β super family member protein and maintain biological activity.

Contrary to these arguments Keck et al. and Qian et al. swap domains between different TGF- β super family members and retain the biological activity. Furthermore, the teachings in combination provide the motivation to one of ordinary skill in the art at the time of filing to modify the TGF- β super family because the sequences for the finger and heel regions may be swapped from the respective finger and heel region sequences of any known member of the TGF- β super family. In addition, the use of chimeric molecules would be a practical approach to investigating the structure/function relationships of OP-1 and CDMP-2, and the only stable form in solution of such a chimeric molecule would reasonably be expected to be a dimer.

Applicants argue that the Keck reference only teaches a single chain protein and not the dimeric protein. As indicated in Paper No: 16 (page: 5), one cannot show nonobviousness by attacking references individually where the rejections are based on combination of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Further Applicants argue that nothing in Keck teaches or suggests a dimeric or chimeric TGF- β super family member protein wherein one monomer comprises a CDMP-2 finger 2 subdomain and finger 1 and heel subdomains from a second member of the superfamily. As previously indicated in Paper No: 16 (page: 6, last paragraph), Daopin teaches the close structural similarity between TGF- β 2 and BMP-2, and suggests that the only stable form of TGF- β 2 in solution is a dimer. In addition, Keck reference does indicate that the TGF- β superfamily members are only active in their dimeric confirmation (column 10, lines 41-42). It would have been obvious to one of ordinary

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skill in the art at the time of Applicants' invention to make a dimer because of the close structural similarity between TGF- β 2 and BMP-2 and the only stable form of TGF- β 2 is a dimer.

Applicants argue that Luyten does not identify the finger 1, heel, and finger 2 regions and the reference does not teach or suggest chimeric proteins. Applicants' arguments haven fully considered and fully addressed in Paper No: 16 (page: 5, last paragraph). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants also argue that Griffith does not teach or suggest the dimeric chimeras. Applicants' arguments haven fully considered and fully addressed in Paper No: 16 (page: 6, 2nd paragraph).

In addition, Applicants argue that Qian does not teach the claimed polypeptide. Furthermore, it is argued that the Qian reference only teaches a chimeric protein containing the subdomains from the same member of the super family. Applicants' arguments haven fully considered and fully addressed in Paper No: 16 (page: 7, 1st paragraph). In addition, it also teaches the formation of a functional chimera of TGF- β 2-TGF- β 1- TGF- β 2 subdomains.

Applicants argue that Daopin does not teach or suggest the chimeras TGF- β super family members. Applicants' arguments haven fully considered and fully

addressed in Paper No: 16 (page: 7, 2nd paragraph). In the present case at least Keck identifies the finger 1, heel and finger 2 regions and teaches making chimeric monomers that are chimeras of the finger 1, heel, and finger 2 regions.

Applicants argue that there is no teaching or suggestion to combine the references and there is no motivation to combine the references. Applicants' arguments haven't fully considered and fully considered but they are not persuasive. Keck provides specific guidance as to the particular form of the claimed invention and how to achieve it. Qian provides a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimera because CDMP-2 has chondrogenic activity *in vivo* but substantially no osteogenic activity and an OP-1/CDMP-2 chimera would provide a practical approach to investigate structure/function relationships of chondrogenic versus osteogenic activity. In addition Qian teaches the formation of a chimera without linkers that have specific biological activity.

5. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for

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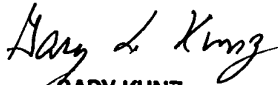
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the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

js
June 13, 2003


GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600